REMARKS

Claims 21-35 are pending in the application and have been examined. The Examiner's allowance of Claims 22-27 is noted with appreciation. Claims 21, 28, and 32 stand rejected and Claims 29-31 and 33-35 are objected to. Applicants respectfully request reconsideration and allowance of Claims 21-35.

The Rejection of Claims 21, 28, and 32 Under 35 U.S.C. § 103

Claims 21, 28, and 32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,968,477, issued to Kasina et al., in view of Giblin et al. (1997) *Bioconjugate Chem.* 8:347. Applicants respectfully traverse the rejection for the following reasons.

Claim 21 relates to an isolated nucleic acid molecule that encodes a modified annexin having an N-terminal chelation site comprising the amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys. Claim 28 relates to a replicable expression vector that includes a nucleic acid sequence that encodes the modified annexin. Claim 32 relates to a host cell that includes the vector of Claim 28.

The Examiner states that the claimed invention includes a chelating moiety that reads on N_xS_y, specifically that the recited sequence X_1-Gly-X_2 reads on the N_xS_y chelating moiety where the N is provided by the Gly and the S is provided by the Cys. As an initial matter, applicants note that the claimed invention does not include a chelating moiety. The claimed invention relates to an isolated nucleic acid (vector and host cell) that encodes a modified annexin. Although the modified annexin can in some way be considered to include an "N_xS_y" chelating moiety, the Kasina reference does not teach, suggest, or provide any motivation to make the claimed invention because the modified annexin encoded by the nucleic acid molecule of the invention includes an N-terminal chelation site comprising the amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The conjugates described by the Kasina reference are structurally dissimilar from the recited modifed annexin and do not include an N-terminal chelation site comprising the amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys.

The Examiner has directed applicants to Col. 3, lines 10-18, where the Kasina reference provides a description of preferred conjugates of the invention. At Col. 3, lines 8-23, three conjugates are described:

(1) a first conjugate that includes an annexin and an esterase-sensitive N_xS_y chelating compound conjugated to the annexin;

(2) a second conjugate that includes a modified annexin, wherein the modification provides an accessible sulfhydryl group, and an N_xS_y chelating compound conjugated to the annexin; and

(3) a third conjugate that includes a modified annexin, wherein the modification provides an accessible sulfhydryl group, and an esterase-sensitive N_xS_y chelating compound conjugated to the annexin.

The first and third conjugates include an esterase-sensitive N_xS_y chelating compound. The reference describes such esterase-sensitive chelates at Col. 22, line 27 through Col. 23, line 3. These chelates include one or more ester groups that cleaved during metabolism in the liver. The reference notes that such chelates are described in U.S. Patent No. 5,112,953 and illustrates one such chelate at Col. 22, lines 51-63. The claimed invention relates to a nucleic acid molecule that encodes a modifed annexin that does not include an esterase-sensitive chelate. The recited modified annexin has an N-terminal chelation site comprising the amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys. Such a chelation site is not suggested by the reference.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The second conjugate described in the Kasina reference noted above includes a modified annexin and an N_xS_y chelating compound conjugated to the annexin, wherein the modification provides an accessible sulfyhydryl group. (Emphasis added.) Therefore, the second conjugate described in the Kasina reference noted above includes a modified annexin having an accessible sulfhydryl group and an N_xS_y chelating compound. The claimed invention relates to a nucleic acid that encodes a modifed annexin that does not include an accessible sulfhydryl group and an N_xS_y chelating compound. The recited modified annexin has an N-terminal chelation site comprising the amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys. Such a chelation site is not suggested by the reference.

The claimed invention is directed to isolated nucleic acid molecules and vectors (and host cells that include the vector) encoding a polypeptide that bears no structural similarity to the conjugates described in the Kasina reference. The Kasina reference fails to teach, suggest, or provide any motivation to make the claimed invention: a nucleic acid molecule that encodes a modified annexin having an N-terminal amino acid extension that includes an amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys.

The Examiner states that the chelating moiety reads on the N_xS_y chelating compound described in the Kasina reference. Applicants respectfully disagree. The modified annexin recited in the claimed invention has an N-terminal amino acid extension that includes an amino acid sequence X_1-Gly-X_2, wherein X_1 and X_2 are selected from Gly and Cys, and wherein at least one of X_1 or X_2 is Cys. None of the N_xS_y chelating compounds described in the reference met the requirements of the recited modified annexin. None of the N_xS_y chelating compounds described in the reference the includes a Cys moiety. There are only two non-aromatic chelating

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

compounds described in the reference: the first compound is illustrated at Col. 22, lines 51-63 (same compound also illustrated in Example XIII) and the second compound is illustrated at Cols. 53 and 54, line 26. Neither compound includes a Cys moiety (which requires the presence of an alpha-amino group) and the second compound does not include either a Cys moiety or a Gly moiety. See FIGURES 1A, 1B, and 1C of the present application for the chemical structures representative N-terminal chelation sites including Gly and Cys moieties.

Applicants submit that the mere disclosure of N_xS_y chelating compounds, particularly N_xS_y chelating compounds having no other structural similarity to the recited modified annexins, does not render obvious other chelating compounds that satisfy this broadly defined and arbitrary nomenclature.

Because the conjugates of the Kasina reference are structurally dissimilar from the modified annexin recited in the claimed invention, the Kasina reference fails to teach, remotely suggest, provide any motivation to make, or otherwise render obvious the claimed invention.

The Giblin reference describes a modified alpha-melanotropin that includes an N-acetyl-Cys-Gly-Cys-Gly moiety. The reference provides no teaching, suggestion, or motivation to make a nucleic acid molecule encoding a modified annexin as in the claimed invention.

The cited references provide no suggestion or motivation to combine their respective teachings. Even if the teachings of the cited references were combined, because of the teaching of the Kasina reference regarding the requirements of the conjugates noted above, the result would not be the claimed invention.

Because the cited references, either alone or in combination, fail to teach, suggest, provide motivation to make, or otherwise render obvious the claimed invention, applicants

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

submit that the claimed invention is nonobvious and patentable over the cited references. Withdrawal of this rejection is respectfully requested.

The Rejection of Claims 21, 28, and 32 Under 35 U.S.C. § 103

Claims 21, 28, and 32 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Kasina reference in view of U.S. Patent No. 5,849,261, issued to Dean et al. Applicants respectfully traverse the rejection for the following reasons.

For the reasons noted above, the Kasina reference fails to teach, remotely suggest, provide any motivation to make, or otherwise render obvious the claimed invention.

The Dean reference describes modified VIP peptides that include Gly-Gly-Cys and Cys-Gly-Gly moieties. The Dean reference provides no teaching, suggestion, or motivation to modify an annexin to include such a moiety.

The cited references provide no suggestion or motivation to combine their respective teachings. Even if the teachings of the cited references were combined, because of the teaching of the Kasina reference regarding the requirements of the conjugates noted above, the result would not be the claimed invention.

Because the cited references, either alone or in combination, fail to teach, suggest, provide motivation to make, or otherwise render obvious the claimed invention, applicants submit that the claimed invention is nonobvious and patentable over the cited references. Withdrawal of this rejection is respectfully requested.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Conclusion

In view of the above amendments and foregoing remarks, applicants believe that, in addition to Claims 22-27, Claims 21 and 28-35 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone the applicants' attorney at 206.695.1755.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]

George E. Renzoni, Ph.D.
Registration No. 37,919
Direct Dial No. 206.695.1755

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the below date.

Date: June 7, 2004

GER:KBB\cj\md

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100